REMARKS

I. Claims Rejections under 35 U.S.C. § 103

A. Claims 1, 9 and 27-34 are Patentable over Omoigui in view of Muller.

Claims 1, 9 and 27-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Omoigui (U.S. 2004/0038874, "Omoigui") in view of Muller, *et al.* (U.S. 6,020,358, "Muller") (Office Action, page 3). Applicant respectfully disagrees.

The instant claims recite, *inter alia*, methods of treating complex regional pain syndrome using a specific compound, (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. As demonstrated in Applicant's response to the Office Action dated December 12, 2007, the art cited by the Examiner does not teach or suggest the use of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for treating complex regional pain syndrome as recited in the instant claims.

Specifically, the Examiner maintains that, although Omoigui and Muller do not teach the use of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for treating complex regional pain syndrome ("CRPS"), one of ordinary skill in the art would allegedly have been motivated to use this compound to treat CRPS because the compound is "disclosed by Muller to be useful in lowering TNF-α levels in a subject." (Office Action, page 4). The Examiner further states that the rationale for combining Omoigui and Muller is not based on structural similarity, which Applicant reasserts is lacking, but primarily on "shared biological function as TNF-α blockers." (*Id.*). If this assertion were true, any and all compounds having *in vitro* TNF-α activity would be obvious to use in treating CRPS. In other words, the Examiner appears to be making the broad generalization that it would be obvious to treat any disease or disorder associated with TNF-α with any compound disclosed to be a TNF-α inhibitor, regardless of the thousands of possible variations thereof. (Office Action, page 5). Clearly this cannot be the rejection the Office is asserting.

Indeed, the mere "identification in the prior art of each component of [an invention] does not show that the combination as a whole...is obvious." *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). Rather, "the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention." *Id.* (Emphasis added). The

Examiner's bare allegation that motivation to combine Omoigui and Muller exists because each reference discloses TNF-α inhibitors does not meet the legal requirement for a *prima facie* case of obviousness. (Office Action, page 5); *See Eli Lilly*, 471 F.3d at 1379.[1]

The Examiner further alleges that the holding of *KSR Int'l Co. v. Teleflex Inc.* 127 S.Ct. 1727 (2007), supports his claim that the combination of the specific compound and specific disorder of the instant claims is obvious. (Office Action, pages 5-6). Applicant disagrees. *KSR* did not overrule the result of *Eli Lilly v. Zenith Goldline Pharmaceuticals*, as cited above, or any other case holding that there must be a reasonable expectation of success in order for one skilled in the art to be motivated to try every possible combination disclosed in the prior art. *See Medichem, S.A. v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006); *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). Indeed, reasonable expectation of success is upheld in *KSR*. *See KSR*, 127 S.Ct. at 1739 and 1742 (an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results"). Moreover, in the passage quoted by the Examiner, and contrary to the Examiner's position, the Supreme Court itself mentions an "anticipated success" that must be present in order for a combination to be "obvious to try." (Office Action, pages 5-6, *citing KSR.*, 127 S.Ct. at 1742).

Following the *KSR* decision, the Federal Circuit has based determinations of obviousness on whether a claimed combination would have yielded "predictable results" or whether there would have been "a reasonable expectation of success" in the claimed invention. *See e.g. In re Trans Tex. Holdings Corp*, 498 F.3d 1290 (Fed. Cir. 2007) (determination of obviousness for a patent relating to stem cell research based on whether the combination yielded "predictable results."); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007) (patent challenger must show by "clear and convincing evidence" that there would have been a "reasonable expectation of success."); *Aventis Pharma Deutschland GmbH v. King Pharms, Inc.* 499 F.3d 1293, 1301 (Fed. Cir. 2007) (determination of obviousness based on whether the prior art provided an "expectation" that claimed compounds would have the intended properties.).

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[1] Applicant points out that claims 32-34, which recite specific dosages of the claimed compound, are certainly not obvious in view of the references cited by the Examiner.

Here, the Examiner has failed to show any sign of a "reasonable expectation of success" or "anticipated success" based on the broad disclosures of Omoigui and Muller. In *KSR*, the obvious combination was the use of known electronic controls in combination with a mechanical gas pedal. *KSR*, 127 S.Ct. at 1729. The court also cited multiple references that taught how the two elements could be combined to reach the claimed device. *Id.* at 1744-45. Here, the Examiner has failed to provide any reference that teaches the combination of the specific compound of the instant claims to treat CRPS. Furthermore, the combination of mechanical and electrical elements in *KSR* is not at all analogous to the selection of a particular chemical compound for use in treating a specific disorder in a patient. As discussed in Applicant's previous response, the courts have long recognized the unpredictability of the biological properties of chemical compounds. *See In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties..."). Simply put, one of ordinary skill in the art would not reasonably expect that every compound with TNF-α activity would be useful in treating CRPS. Therefore, without a more explicit teaching in the prior art of the instantly claimed method, one of ordinary skill in the art would have no motivation to test each and every compound disclosed in Muller to treat each and every disease or disorder disclosed in Omoigui.

In the instant case, to the extent Muller directs one to experiment with hundreds of phenethylsulfone compounds represented by formula I (Columns 5-6), Muller can not be read to focus on the racemic compound 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, much less the (+)-isomer recited in the instant claims. Omoigui discloses that thalidomide and analogues mainly inhibit TNF-α, without identifying any thalidomide analogues. (Paragraph [0023]). There is no teaching or suggestion in Omoigui as to the recited (+)-isomer within the instant claims. Thus, the combined teachings fail to provide an objective basis for obviousness, and do not provide a reasonable expectation that the (+)-isomer of the instant claims could be successfully used in treating CRPS. Without such specific guidance in the cited art, one of ordinary skill in the art would not reasonably expect that the instant (+)-isomer can be used for treating CRPS as in the claimed invention.

Further, the scope of the instant claims is in stark contrast with the breadth and general teachings of Muller where hundreds of compounds are described. Specifically, Muller teaches a genus of compounds represented by general Formula I, which can be replaced by various substituents at various positions. The combinations of the possible

substituents (*e.g.*, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{8'}$, $R^{9'}$, R^{10}, and $R^{10'}$) in Formula I would lead to hundreds of compounds (Columns 5-6). Muller does not provide one of ordinary skill in the art with any suggestion or motivation to single out the specific racemate to which the recited (+)-isomer belongs. The mere fact that a species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994); *see also In re Brouwer*, 77 F.3d 422, 425, 37 U.S.P.Q.2d 1663, 1666 (Fed. Cir. 1996) (the mere fact that one species selected from a genus could be modified or replaced to reach the claimed invention does not render the claims obvious unless the prior art suggested that modification or replacement); MPEP § 2144.08. While Muller does disclose a racemic compound in Example 12, Muller viewed as a whole does not focus on this racemic compound among the hundreds of compounds recited therein. In other words, to the extent that one of ordinary skill in the art would have been led to improve the compounds of Muller, they would have been just as likely to look at completely different compounds or modifications thereof, as opposed to resolution of the racemate of Example 12. Thus, Muller does not provide a "finite number of identified, predictable solutions," but a "broad selection of compounds any of which could have been selected as the lead compound for further investigation." *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350, 1356, 1359 (Fed. Cir. 2007). There is no adequate support in the prior art for the selection of the recited (+)-isomer in treating the specific disease CRPS to establish a *prima facie* case of obviousness. *Id.*

Furthermore, a specific isomer or its uses can be patentably distinct from its racemate. The Federal Circuit has specifically addressed the issue of whether a single enantiomer of a pharmaceutical compound can be nonobvious in view of a prior art disclosure of the compound's racemate, and affirmed the patentability of individually resolved chiral pharmaceutical compounds. *See Forest Labs., Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007) (*aff'g* 438 F.Supp.2d 479); *see also In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978). Thus, even assuming, *arguendo*, that one of ordinary skill in the art would select the racemate of Example 12, Applicant submits that the instant claims, which recite (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for treating CRPS, are not obvious over Muller.

Additionally, it is well known to those ordinary skilled in the chemical and pharmaceutical arts that the separation and/or preparation of specific isomers is not

predictable, nor are these processes always routine. *See, Forest*, 438 F.Supp.2d at 493; J. Darrow, "The Patentability of Enantiomers: Implications for the Pharmaceutical Industry," 2007 Stanford Tech. L. Rev. 2, ¶56 ("the process for making the racemate may not make obvious a process for resolving the racemate."). Moreover, whether a specific stereoisomer has improved biologically activity or a more desirable pharmacological profile is recognized as unpredictable in the art. *See In Re May* at 1092; *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, at 754 (the prior art suggested unpredictability in the degree of activity exhibited by a specific enantiomer); *see also Ex Parte Bonfils*, 64 U.S.P.Q.2d 1456, 1461 (B.P.A.I. 2002).[2] Muller provides no preference for the biological or pharmacological activity of the compound of Example 12, much less any indication of the activity of the specific (+)-isomer for treating pain as recited in the instant claims.

Without such specific guidance in the cited art, one of ordinary skill in the art would have no motivation to select the specific (+)-isomer recited in the instant claims. Without such motivation, a *prima facie* case of obvious cannot be made.

B. Claims 2-5 and 23 are Patentable over Omoigui in view of Muller and Merck.

Claims 2-5 and 23 stand rejected under 35 U.S.C. § 103(a) as unpatentable under Omoigui in view of Muller, further in view of Merck. (Office Action, page 6). The Examiner alleges that because Merck discloses that certain drugs, physical therapy and/or surgery can be used to treat CRPS, one skilled in the art would be motivated to combine this knowledge with the teachings of Omoigui and Muller, discussed above, to practice the methods of claims 2-5 and 23. (*Id.*). Applicant respectfully disagrees.

As discussed above, Omoigui in view of Muller does not teach or suggest the use of the specific compound as recited in instant claim 1 to treat CRPS. *Supra*, pages 2-5. Merck does not cure this defect. Merck does not disclose or suggest anything about (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione or its use in treating CRPS, much less a combination with another drug or therapy as claimed.

The Examiner has identified no teaching or suggestion that the recited compound may be used in treating pain, much less CRPS, much less the combination therapy. Nowhere does Muller or Merck suggest or motivate the use of the recited compound with an additional agent or therapy for treating pain, let alone CRPS. Thus, one of ordinary

[2] *Bonfils* is a nonprecedential decision.

skill in the art would not have had a reasonable expectation of success from Omoigui, Muller and Merck. A *prima facie* case of obviousness has not been established and the rejection must be withdrawn.

II. Obviousness-Type Double Patenting Rejections

Claims 1, 9 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either claims 1, 6, 12 and 17 of U.S. Patent No. 6,020,358 ("the '358 patent"), or claims 1, 4, 10 and 15 of U.S. Patent No. 6,011,050 ("the '050 patent") in view of Omoigui. (Office Action, page 8). Applicant respectfully disagrees.

Obviousness-type double patenting is a judicially created doctrine intended to prevent improper timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent. *See In re Braat*, 19 U.S.P.Q.2d 1289, 1291-92 (Fed. Cir. 1991). In *General Foods Corp. v. Studiengesellschaft Kohle mbH*, the Federal Circuit further explained that in an obviousness-type double patenting rejection "it is important to bear in mind that comparison can be made only with what invention is claimed in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim defines and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." 23 U.S.P.Q.2d 1839, 1845 (Fed. Cir. 1992).

As discussed above, the instant claims are drawn to methods for treating a specific disease, CRPS, with a specific compound. The claims of the '358 and '050 patents recite methods of reducing undesirable levels of TNF-α without any reference to CRPS. The claims of the '358 and '050 patents provide no suggestion or motivation for one skilled in the art to select the specific compound from the genera disclosed therein, and certainly not to treat the specific disease, CRPS. By arguing to the contrary, the Examiner has improperly ventured beyond what the claims of the '358 and '050 patents define.

The Examiner cites *In re Fulton* for the proposition that the disclosure of more than one alternative in a prior art reference does not constitute a "teaching away" from any of the alternatives. (Office Action, page 10). Applicant does not take the position that the claims of the '358 and '050 patents "teach away" from the present invention, but that the sheer number of compounds of the claims of the '358 and '050 patents render the instant claims nonobvious without further guidance to select the specific compound for treating the specific disease of the instant claims. Because the Examiner has failed to

point out anything in the claims of the '358 and '050 patents that would aid one skilled in the art to arrive at the specific compound of the instant claims, the claims of the '358 and '050 patents are simply too broad to support the Examiner's double patenting rejection.

The Examiner further argues that "the number of different species recited by a reference does not render any individual species unavailable to one of ordinary skill in the art." (Office Action, page 10). To the contrary, it is settled law that the mere fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *See Baird*, 16 F.3d at 382; *see also Brouwer*, 77 F.3d at 425; MPEP § 2144.08. Indeed, the Federal Circuit's predecessor has held that a genus of 259 compounds was sufficiently large to avoid anticipation of a species. *In re Ruschig*, 343 F.2d 965, 974-75, 145 USPQ 274, 282 (C.C.P.A. 1967). The claims of the '358 and '050 patents encompass hundreds of compounds. Because the specific compound of the instant claims is not obvious over the broad genera of the claims of the '358 and '050 patents, the instant claims are patentably distinct from those claims. For this reason alone, the Examiner's double patenting rejection must be withdrawn.

Furthermore, the double patenting rejection must be withdrawn because the claims of the '358 and '050 patents do not disclose, teach or suggest CRPS. As discussed above, Omoigui merely mentions CRPS among many different pain disorders, and the Examiner has failed to demonstrate why one skilled in the art would select CRPS from the many diseases and disorders of Omoigui and apply that teaching to the claims of the '358 and '050 patents to arrive at the presently claimed invention. Without demonstrating why one skilled in the art would be motivated to make this specific selection, the instant claims cannot be obvious over the claims of the '358 and '050 patents patent in view of Omoigui. *See KSR*, 82 U.S.P.Q.2d at 1395 (Examiner must "identify a reason that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does."). The claims of the '358 and '050 patents in view of Omoigui do not teach or suggest a method of treating CRPS, much less doing so with (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. For these reasons, the instant claims are patentably distinct from the claims of the '358 and '050 patents, and the double patenting rejection must be withdrawn.

Applicant reasserts that the policy behind a double patenting rejection—the prevention of an unjustified extension of the term of a patent—is not served by the Examiner's rejection in this case. *See In re Braat*, 19 U.S.P.Q.2d at 1291-92; *see also In re Kaplan*, 789 F.2d 1574, 1579 (Fed. Cir. 1986) ("the basis for...obviousness-type

double patenting rejections is timewise extension of the patent right"). Allowance of the instant claims, directed to the treatment of a disease not specifically claimed in the '358 and '050 patents, would not result in the timewise extension of the terms of these patents.

In sum, Applicant respectfully submits that the rejection of the pending claims under obviousness-type double patenting should be withdrawn because no *prima facie* case of obviousness has been established for the pending claims over any of the claims of the cited patents. Applicant further submits that no terminal disclaimer over the cited patents is necessary.

Conclusion

In view of the foregoing remarks, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

A fee for an extension of time for a period of two months is required. The fee will be paid via EFS Web. The Commissioner is hereby authorized to charge any additional required fee under 37 C.F.R. § 1.17, or any other required fee, or any credits, to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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